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Case Report

Nephrotic syndrome in hand, foot and mouth disease caused by coxsackievirus A16: a case report

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SUMMARY

Some viruses, including certain members of the enterovirus genus, have been reported to cause nephrotic syndrome. However, no case of coxsackievirus A16 (CVA16)-related nephrotic syndrome has been reported so far. We describe a case of CVA16-related hand, foot and mouth disease presenting with nephrotic syndrome in a 3-year-old boy. This is the first report of CVA16-related nephrotic syndrome.

1. Introduction

Coxsackievirus A16 (CVA16), a member of the Enterovirus A species, is a common causative pathogen of hand, foot and mouth disease (HFMD). Most CVA16-related HFMD cases are mild, with rashes, fever, or an acute respiratory infection; only a few present complications of the central nervous system. Many pathogens have been reported to cause nephrotic syndrome or glomerulonephritis. Some members of the Enterovirus B species have also been reported to cause glomerulonephritis,[1] however to our knowledge, no coxsackievirus A16 (CVA16)-associated nephrotic syndrome or glomerulonephritis has been reported so far. We describe a case of CVA16-related HFMD presenting with nephrotic syndrome in a 3-year-old boy.

1.1. Case report

A previously healthy 3-year-old Cantonese boy was hospitalized for generalized rashes, eyelid edema, and oliguria. Three days before admission, a maculopapular rash with blisters in the center had appeared on his hip and this had then spread to the palms of his hands and feet over the following 2 days. Swelling of the eyelids and oliguria began to appear a day before admission. Before admission the boy had presented no fever, but had occasionally emitted a single cough. His past medical history showed no record of kidney disease.

A physical examination done on admission revealed hypertension (109/63 mmHg) and a normal temperature, pulse rate, and breathing rate. Moderate edema was noted in the eyelids, rather than in other parts of the body. Conspicuous dark red maculopapular rashes on hip, palms and feet, vesicles in mouth cavity membrane were observed. Rough breathing sounds were heard on auscultation. No other abnormality was found during the admission physical examination.

Urinalysis revealed moderate hematuria (red blood cell count (RBC) 35×10^6/l), mild leukocyturia (white blood cell count (WBC) 12×10^6/l), and severe proteinuria (proteinuria 4+). The specific gravity of the urine was within the normal range. Severe hypoalbuminemia (11.3 g/l) and mild hyperglobulinema (37.0 g/l) were found in the admission tests. The following serum lipid values suggested hyperlipidemia: total cholesterol 7.48 mmol/l, total triglyceride 2.76 mmol/l, high density lipoprotein cholesterol (HDL-C) 1.65 mmol/l, low density lipoprotein cholesterol (LDL-C) 5.38 mmol/l, lipoprotein a (Lpa) 2407 mg/l, apolipoproteins A1 (ApoA1) 2.11 g/l, apolipoproteins B (ApoB) 1.93 g/l. Admission tests also showed slight hypocalcemia (1.98 mmol/l), mild azotemia (8.0 mmol/l), and an elevated erythrocyte sedimentation rate (80 mm/h). No other abnormality was found for the admission tests.

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The boy was administered low molecular weight dextran and furosemide on the day of admission due to oliguria and edema. His urine output responded to treatment with a jump from 353 ml/24 h on the day of admission to approximately 1100 ml/24 h on the other days, except for 770 ml/24 h on day 16 of hospitalization. The edema grew worse on the day following admission, with the appearance of facial edema and pitting edema in the lower extremities; the edema then resolved gradually and disappeared on day 7 of hospitalization. However, the edema reappeared on day 16 of hospitalization and eventually disappeared completely on day 21 of hospitalization. The highest blood pressure observed during the hospitalization was 118/78 mmHg. During his 27-day hospitalization, the patient was also treated with bed rest, human immunoglobulin, acyclovir, methylprednisolone, atomization inhalation, and supportive treatments. Urinalysis showed a trend of gradually declining protein, WBC, and RBC in the urine, and these eventually reverted to normality on day 21 of hospitalization. The total content of urine protein was 2801 mg/24 h on day 4 of hospitalization. The boy was eventually discharged without hypertension, edema, or cough. On the day of discharge, all serum biochemical tests were normal except for slightly low levels of albumin (33.3 g/l) and total protein (52.4 g/l). The total content of 24 h urine protein was normal at 35.2 mg/24 h on the day before discharge. During the 2-year follow-up he showed no recurrence of edema, hypoproteinemia, hyperlipidemia, or hypertension, however there was a relapse of slight proteinuria (+ to ++) and microscopic hematuria occurred now and then.

Other relevant tests and examinations during his hospitalization were the following: real-time reverse transcription PCR (RT-PCR) test results from a stool sample were positive for pan-enterovirus and CVA16, and negative for enterovirus 71. Genotyping of sequenced viral protein 1 (VP1) further confirmed the CVA16 infection. PCR was negative for both Epstein–Barr virus (EBV) and cytomegalovirus (CMV) in blood. Testing for hepatitis B virus (HBV) showed 0 IU/ml level of hepatitis B surface antigen (HBsAg) (0 IU/ml–0.05 IU/ml) and 324.03 mIU/ml level of anti-HBsAg antibody (HBsAb) (0 mIU/ml–10 mIU/ml). Both antinuclear antibody and anti-double-stranded DNA antibodies were negative. Serum testing also showed C3 and C4 complement, titers of rheumatoid factor, anti-streptolysin O antinuclear antibody (ANA), and anti-DNA antibody to be within the normal ranges.

2. Discussion

We have presented a case of CVA16-related nephrotic syndrome secondary to HFMD. The positivity for CVA16 and typical HFMD rash distribution suggested CVA16-related HFMD. The manifestations of hematuria, leukocyturia, edema, oliguria, massive proteinuria (2801 mg/24 h), hypoalbuminemia (11.3 g/l), and hyperlipidemia (cholesterol 9.05 mmol/l, triglycerides 2.76 mmol/l) in this 3-year-old child meet the diagnostic indices of nephrotic syndrome. Combined with the presentations of hypertension, azotemia, and microscopic hematuria, the case is consistent with a nephritis type of nephrotic syndrome.

Since the response to treatment was good, with obvious improvements in clinical and laboratory manifestations, a renal biopsy was not performed to acquire the pathology type and to provide pathological evidence ascertaining CVA16 as the incontrovertible pathogen causing the nephrotic syndrome in this case. Establishing CVA16 as the causative pathogen of nephrotic syndrome in this case was based on the following evidence: CVA16 positivity, negative renal disease history, occurrence of oliguria lagging 2 days behind eruptions, normal levels of rheumatic factor, anti-streptolysin O, and antinuclear antibody, and negativity for antinuclear antibody, anti-double-stranded DNA antibody, HBV, CMV, and EBV. Due to the presence of CVA16 and the ruling out of possible pathogenic factors for glomerulonephritis in a Cantonese patient (autoimmune diseases, Streptococcus, HBV, and EBV), the CVA16 infection was deemed to be the most likely pathogenic factor for nephrotic syndrome in this case.

Members of coxsackievirus B have been reported to be causative pathogens of glomerulonephritis.[1] A pathological study has shown that coxsackieviruses B1–6 can produce cytopathic effects in human proximal tubular epithelial cells and podocytes.[2] Coxsackievirus and adenovirus receptor (CAR), a widely expressed transmembrane protein that could serve as a receptor for coxsackievirus B, is expressed on the cell membrane from the kidney.[3] Similar to coxsackievirus B, CVA16 also has a ubiquitously expressed receptor in human tissue, namely scavenger receptor class B member 2 (SCARB2).[4] The ubiquitously expressed SCARB2 means that CVA16 also has a chance of binding to cells of the kidney, causing kidney diseases. African green monkey kidney cells (Vero) are used widely for culturing and isolating enteroviruses, including CVA16. As the evidence above suggests that CVA16 can cause a cytopathic effect by direct infection as does coxsackievirus B, the pathophysiological mechanism by which the nephritis type of nephrotic syndrome was caused in this case may be as follows: the cytopathic and lytic effects caused by direct CVA16 infection damaged the proximal tubular epithelial cells and molecular barrier of the glomerular filtration membrane and charge barrier, leading to manifestations of proteinuria, hematuria, leukocyturia, and hypoalbuminemia in the acute phase, while the relapse of slight proteinuria and microscopic hematuria was likely caused by precipitated immune complex-related glomerular injury. Although the incidence of CVA16 is higher than that of any member of coxsackievirus B in many countries, to our knowledge, no CVA16-related glomerulonephritis or nephrotic syndrome has been reported so far. This may be due to factors including the viral load in blood, density distribution of receptors in other organs, complex interactions between immunity and virus, and reproduction capacity in cells of the glomerulus. In fact, kidney disease caused by enterovirus is not unusual, and a study on 10 patients with IgA nephropathy detected enterovirus in three out of 10 biopsies.[5] To our knowledge, this is the first case report of glomerulonephritis caused by CVA16.

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